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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte DAVID LEWIS, DAVID GANDERTON, BRIAN MEAKIN,
PAOLO VENTURA, GAETANO BRAMBILLA, and
RAFFAELLA GARZIA

Appeal 2009-005022
Application 10/612,072
Technology Center 1600

Decided: September 16, 2009

Before TONI R. SCHEINER, RICHARD M. LEBOVITZ, and
FRANCISCO C. PRATS, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 11-14, 16-19, 21-26, 28-32, 35-46, 48, and 49, all the claims pending. We have jurisdiction under 35 U.S.C. § 6(b).

BACKGROUND

"For many years the preferred propellants used in aerosols for pharmaceutical use have been a group of chlorofluorocarbons [CFCs]" (Spec. 1: 22-24), but CFCs "have been implicated in the destruction of the ozone layer and their production is being phased out" (*id* at 1: 29 to 2: 2). Hydrofluoroalkane (HFA) propellants "are considered less destructive to ozone and these are proposed as substitutes for CFCs" (*id.* at 2: 3-6), particularly HFA 134a and HFA 227 (*id.* at 2: 7-9).

According to the Specification, "chemical stability problems of active ingredients in solution in HFA propellants can be eliminated by . . . employing metered-dose inhalers [MDIs] having part or all of their internal metallic surfaces consisting of stainless steel, anodised aluminium or . . . an inert organic coating" to store and deliver the solutions (Spec. 4: 26 to 5: 3).

STATEMENT OF THE CASE

"The invention relates to the use of pressurised metered dose inhalers (MDIs) having part or all of their internal surfaces consisting of stainless steel, anodised aluminium or . . . an inert organic coating. The invention also relates to compositions [containing solubilized budesonide] to be delivered with said MDIs" (Spec. 1: 3-8).

Claims 11, 19, 35, and 37 are representative of the subject matter on appeal:

11. An aerosol formulation comprising budesonide, a propellant vehicle, and an antioxidant,

wherein said budesonide is completely dissolved in the propellant vehicle and said propellant consists of one or more hydrofluroalkanes and a cosolvent.

19. A pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized aerosol formulation comprising

budesonide, a propellant vehicle, and an antioxidant, wherein said budesonide is completely dissolved in the propellant vehicle and said propellant consists of one or more hydrofluroalkanes and a cosolvent.

35. The pressurized metered dose inhaler according to claim 19, wherein at least a part of the inner surfaces of said pressurized metered dose inhaler is composed of stainless steel.

37. The pressurized metered dose inhaler according to claim 19, wherein at least a part of the inner surfaces of said pressurized metered dose inhaler is composed of anodized aluminum.

The Examiner relies on the following evidence:

Tzou	US 5,776,433	Jul. 7, 1998
Cutie	US 6,129,905	Oct. 10, 2000
Riebe	US 6,558,651 B1	May 6, 2003
Lewis	US 7,223,381 B2	May 29, 2007

The claims stand rejected as follows:

(A) Claims 11-14, 16-19, 21-26, 28-32, 39-46, 48, and 49 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Cutie and Tzou.

(B) Claims 35-38 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Cutie, Tzou, and Riebe.

(C) Claims 11-14, 16-19, 21-26, 28-32, 35-46, 48, and 49 under the doctrine of obviousness-type double patenting as unpatentable over Lewis.

We affirm rejections (A) and (C), and reverse rejection (B).

OBVIOUSNESS

Issue (A)

The Examiner rejected claims 11-14, 16-19, 21-26, 28-32, 39-46, 48, and 49 as unpatentable over the combined teachings of Cutie and Tzou.

The issue raised by this rejection is whether Appellants have shown that the Examiner erred in concluding that a formulation comprising budesonide, a propellant vehicle, and an antioxidant - where the budesonide is completely dissolved in the propellant vehicle and the propellant consists of one or more hydrofluoroalkanes and a cosolvent - would have been obvious over the disclosures of Cutie and Tzou.

Findings of Fact

FF1 Claim 11 is directed to an aerosol formulation comprising budesonide, a propellant vehicle, and an antioxidant, where the budesonide is completely dissolved in the propellant vehicle and the propellant consists of one or more hydrofluoroalkanes and a cosolvent. Claim 19 is directed to a pressurized metered dose inhaler (MDI) containing the formulation, and claim 26 is directed to a method of treating a bronchial disorder by administering the formulation.

FF2 Hydrofluoroalkanes (HFAs) are "known also as hydro-fluoro-carbons (HFCs)" (Spec. 2: 3-4). "In the compositions to be delivered with the MDIs of the invention the hydrofluorocarbon propellant is preferably selected from the group of HFA 134a, HFA 227 and mixtures thereof" (*id.* at 7: 8-11).

FF3 According to the Specification, "[t]he cosolvent is usually an alcohol, preferably ethanol" (Spec. 7: 12-13).

FF4 Under the heading "Background of the Invention," Cutie teaches that hydrofluorocarbon propellants "are among the leading candidates for replacement of the ozone-damaging [chlorofluorocarbon] CFC propellants." (Cutie, col. 1, ll. 59-61.)

> However, the substitution of an HFC propellant for the CFC propellants in MDI formulations is not straightforward. There are drug solubility, drug stability and deliverability problems as well as particle size issues which must be addressed when substituting propellants in an MDI formulation. MDIs contain drugs which are dissolved or suspended as micronized particles . . . In some solution formulations, a co-solvent may be added to enhance drug dissolution, although this practice may have the disadvantage of decreasing the fraction of the metered dose which may be inhaled and contributing to particle size growth.

(*Id.* at col. 1, l. 61 to col. 2, l. 11.)

FF5 Under the heading "Detailed Description of the Invention," Cutie describes an aerosol formulation "comprising a therapeutically effective amount of at least one drug (active), a sugar and optionally one or more pharmaceutically acceptable excipients, dispersed in . . . at least one hydrofluorocarbon propellant" (Cutie, col. 3, ll. 48-54).

FF6 Cutie teaches that the formulations of his "invention may be suspensions, deagreggated slurries or solutions" (Cutie, col. 3, ll. 60-61).

FF7 According to Cutie, "[t]he sugar acts as a solid diluent/dispersant to aid in the incorporation of the dispersion of or solubilization of actives and excipients in . . . HFC propellants" (Cutie, col. 3, ll. 62-66).

FF8 Cutie's "inventive formulations can be formulated with or without the aid of cosolvents" (Cutie, col. 4, ll. 5-6), and "optional excipients include . . . antioxidants" (*id.* at col. 5, ll. 31-33).

FF9 Drugs which may be administered via Cutie's formulations include budesonide and flunisolide (Cutie, col. 4, ll. 24-25 and 32).

FF10 Budesonide is an acetal corticosteroid, and flunisolide is a chetal corticosteroid (Spec. 8: 21-24).

FF11 Tzou teaches that flunisolide hemihydrate has "appreciable solubility in HFA 134a, HFA 227 or mixtures thereof" (Tzou, col. 1, ll. 52-53), but "[t]his intermediate level of solubility can lead to particle size increase of the drug in a suspension formulation . . . [which] can threaten the utility of a pharmaceutical formulation" (*id.* at col. 1, ll. 58-64).

FF12 Tzou describes "a solution aerosol formulation comprising a therapeutically effective amount of flunisolide, a propellant comprising a hydrofluorocarbon . . . , and ethanol in an amount effective to solubilize the flunisolide in the formulation" (Tzou, col. 1, l. 65 to col. 2, l. 4).

FF13 Tzou teaches that solution formulations eliminate "problems encountered with suspension aerosols such as rapid flocculation, irreversible particle aggregation and bulk separation (creaming or settling); all of which affect dose uniformity" (Tzou, col. 2, ll. 10-14). In addition, Tzou teaches that solubilizing the flunisolide "avoids complications that can occur in certain suspension steroid formulations due to in situ changes in crystal form" (*id.* at col. 2, ll. 44-46).

Principles of Law

When determining whether a claim is obvious, an Examiner must make "a searching comparison of the claimed invention - including all its limitations - with the teachings of the prior art." *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995).

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007).

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that is was obvious under § 103.

Id. at 421. It is proper to "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418. *See also id.* at 421 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton.").

Analysis

Appellants contend that Cutie, "in the section entitled 'Background of the Invention,' . . . discloses a wide variety of aerosol formulations for oral inhalation, including dry-powder formulations, solutions, suspensions, and combination slurry-solutions . . . However, Cutie does not disclose that any of the formulations discussed in the 'Background of the Invention' section contain budesonide" (App. Br. 5).

Appellants contend that "[t]he only time Cutie mentions budesonide is in connection with formulations, which are clearly *not* solutions. Specifically, the only mention of budesonide in Cutie is in connection with the *"inventive"* formulations" (App. Br. 5).

Appellants also argue that "Cutie only mentions antioxidants in connection with dispersion formulations; there is no teaching in this

reference which would suggest adding an antioxidant to a solution formulation" and "[t]here is no mention at all of antioxidants in Tzou" (App. Br. 7).

Appellants' arguments are not persuasive. While it's true that Cutie discusses suspension/dispersion formulations at length, it is not true that he doesn't describe "inventive" solution formulations. Cutie explicitly teaches that budesonide and flunisolide are among the "[d]rugs which may be administered via the inventive formulations" (Cutie, col. 4, ll. 24-33; FF9); that "[t]he formulations of the present invention may be suspensions . . . or solutions" (*id.* at col. 3, ll. 59-61; FF6); that the sugar in the formulations "aid[s] in the incorporation of the dispersion of or in the solubilization of actives and excipients in . . . HFC propellants" (*id.* at col. 3, ll. 62-66; FF7); that his "inventive formulations can be formulated with . . . the aid of cosolvents" (*id.* at col. 4, ll. 5-6; FF8): and that suitable excipients for the formulations include antioxidants (*id.* at col. 5, ll. 31-33; FF8).

Moreover, Tzou emphasizes the numerous advantages of solution formulations over suspension formulations (FF13), and discloses a formulation comprising flunisolide (described as having an intermediate level of solubility in HFC propellants (FF11)), solubilized in an HFC propellant with the aid of ethanol as a cosolvent (FF12).

We agree with the Examiner that the claimed solubilized budesonide formulation would have been obvious given Tzou's teaching that solution formulations have distinct advantages over suspension formulations, and Cutie's teachings that his HFC-based formulations can be solutions containing cosolvents and antioxidants; and that budesonide and flunisolide, both corticosteroids (FF10), can be administered as HFC propellant-based

formulations. Moreover, both Cutie and Tzou provide evidence that one of skill in the art would have expected that solubilizing a drug in an HFC propellant, rather than a CFC propellant, might require a cosolvent, as is the case with flunisolide (FF11, FF12).

Conclusions of Law

Appellants have not shown that the Examiner erred in concluding that a formulation comprising budesonide, a propellant vehicle, and an antioxidant - where the budesonide is completely dissolved in the propellant vehicle and the propellant consists of one or more hydrofluoroalkanes and a cosolvent - would have been obvious over the disclosures of Cutie and Tzou.

The rejection of claim 11 as unpatentable over Cutie and Tzou is affirmed. Claims 12-14, 16-19, 21-26, 28-32, 39-46, 48, and 49 fall with claim 11 as they were not separately argued. 37 C.F.R. § 41.37(c)(1)(vii) (2006).

Issue (B)

The Examiner rejected claims 35-38 as unpatentable over the combined teachings of Cutie, Tzou, and Riebe.

The issue raised by this rejection is whether the Examiner has established that the teachings of the cited art would have led one skilled in the art to load the solubilized budesonide formulation of claim 19 into a pressurized metered dose inhaler lined with stainless steel or anodized aluminum.

Additional Findings of Fact

FF14 Claims 35 and 36 require that the inner surface of the metered dose inhaler of claim 19 is partially or entirely composed of stainless steel,

while Claims 37 and 38 require that the inner surface of the MDI of claim 19 is partially or entirely composed of anodized aluminum.

FF15 Tzou teaches that loading a solublized flunisolide formulation into a canister that has been "coated with a resin that is inert to flunisolide and preferably does not absorb flunisolide from the formulation" (*id.* at col. 4, ll. 8-10) enhances its stability and minimizes its absorption onto the canister walls (*id.* at col. 4, ll. 3-5). Suitable resins include epoxy resins, e.g., epoxy-phenolic resins (Tzou, col. 4, ll. 12-14).

FF16 Riebe teaches that salbutamol sulphate tends to adhere to the inner surfaces of MDIs, particularly in hydrofluoroalkane propellant-based aerosol formulations (Riebe, col. 1, ll. 37-42).

FF17 According to Riebe, the problem of drug adhesion or deposition can be reduced or eliminated by "using a recrystallised form of salbutamol sulphate" (Riebe, col. 1, ll. 47-50). While the recrystallized drug can be loaded into a conventional aluminum can "which may optionally be anodised, lacquer-coated and/or plastic-coated" (*id.* at. col. 5, ll. 24-36), "[a]luminium cans which have their inner surfaces coated with fluorocarbon polymer are particularly preferred . . . [as] such polymer-coated cans can help to reduce even further the deposition or adhesion of salbutamol sulphate on the inner surfaces of the can" (*id.* at col. 5, ll. 27-36).

Analysis

Appellants contend that Reibe is directed to solving deposition and adhesion problems associated with powder formulations of salbutamol sulphate, and there would be no reason for one skilled in the art to turn to Reibe to address the problem of chemical degradation of solubilized budesonide (App. Br. 9).

We agree with Appellants on this point. Tzou teaches that loading a solublized flunisolide formulation into a canister that has been coated with an epoxy resin enhances its stability and minimizes its absorption onto the canister walls (FF15). Riebe is directed to avoiding deposition or adhesion of salbutamol sulphate to the inner surfaces of a canister, primarily by recrystallizing the drug. Riebe teaches that the recrystallized drug can be loaded into an anodized aluminum canister, but "[t]he use of . . . polymer-coated cans can help to reduce even further the deposition or adhesion of salbutamol sulphate on the inner surfaces of the can" (FF17). Not only is Riebe directed to solving problems associated with a crystalline drug form, but coated metal canisters, similar to those already disclosed by Tzou, are preferred. Therefore, we see nothing in Riebe which would have led one skilled in the art to use canisters lined with anodized aluminum or stainless steel in place of the epoxy resin canisters already disclosed by Tzou.

Conclusions of Law

The Examiner has not established that the teachings of the cited art would have led one skilled in the art to load the solubilized budesonide formulation of claim 19 into a pressurized metered dose inhaler lined with stainless steel or anodized aluminum.

The rejection of claims 35-38 as unpatentable over the combined teachings of Cutie, Tzou, and Riebe is reversed.

DOUBLE PATENTING

Issue (C)

The Examiner rejected claims 11-14, 16-19, 21-26, 28-32, 35-46, 48, and 49 under the doctrine of obviousness-type double patenting as unpatentable over claims 1-28 of US Patent 7,223,381 to Lewis.

According to the Examiner, "[t]he difference is that the claims of [the] instant application require an antioxidant, while the claims of '381 do not recite an antioxidant" (Ans. 8).

Appellants contend "[q]uite simply, there is nothing in any of the claims of the '381 patent which would suggest an aerosol formulation which contains an antioxidant" (App. Br. 10).

Appellants' argument is not persuasive. As the Examiner points out, "the language of the reference claims is the open language of comprising and . . . it is known in the art . . . [to] includ[e] an antioxidant in such formulations" as taught by Cutie (Ans. 8 (*see also* FF8)). We agree with the Examiner's conclusion that it would have been obvious for one skilled in the art to include an antioxidant in the claimed budesonide formulation.

The rejection of claims 11-14, 16-19, 21-26, 28-32, 35-46, 48, and 49 under the doctrine of obviousness-type double patenting is affirmed.

SUMMARY

(A) The rejection of claims 11-14, 16-19, 21-26, 28-32, 39-46, 48, and 49 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Cutie and Tzou is affirmed.

(B) The rejection of claims 35-38 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Cutie, Tzou, and Riebe is reversed.

(C) The rejection of claims 11-14, 16-19, 21-26, 28-32, 35-46, 48, and 49 under the doctrine of obviousness-type double patenting as unpatentable over Lewis is affirmed.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED-IN-PART

dm

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